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Synthesis and Evaluation of Biological and Antioxidant Activity of Some New Heterocyclic Compounds of Mefenamic Drug Derivatives

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Abstract

In this study new heterocyclic derivatives were prepared. The most available Mefenamic acid (M) has been reacted with thionyl chloride to get (M1 compound). (M1) compound treated with hydrazinecarboxamide to get (M2) derivative then a ring closer reaction has been made to compound (M2) by NaOH solution to get the 1,2,4-triazole-3-ol ring compound (M3). Compound (M)reaction with phenyl hydrazine hydrate to give (M4) compound then a ring closer reaction have been made using carbon disulfide and hydrazine hydrate in basic media to get (M5) . Compound (M1) treated with 3-aminopropanoic acid to get (M6) compound. (M7) compound has been synthesis by reacting (M6) compound with benzaldehyde in the presence of acetic anhydride to get oxazin ring (M7 compound). The synthesized compounds' antibacterial activity and antioxidant activity (M1-M7) were examined using the (DPPH) technique. The compounds show substantial antioxidant activity equivalent to the well-known (ascorbic acid) (IC50=31.95 g/mL) employed.

Keywords: Mefenamic acid, Hydrazinecarboxamide, Phenylhydrazine, Oxazin, Antioxidant activity

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Introduction

Mefenamic acid (MA) [$C_{15}H_{15}NO_2$] or Ponstan or 2-(2,3-Dimethyl phenyl) amino] benzoic acid is a non-steroidal anti-inflammatory drug (NSAID) used in acute conditions and chronic of inflammation and pain. MA belongs to the aromatic amino acids group (Figure 1) [1]. Mefenamic acid is a derivative of "anthranilic acid", is inhibits proliferation and triggers apoptotic cell death of several human carcinoma cell lines. In addition to the analgesic and antipyretic properties predictable of NSAIDS, MA has been exposed to be effective as therapeutic agent in carcinoma cell lines and Alzheimer's disease [2-5]. Mefenamic acid contains carboxylate and amino groups. It is used as a therapeutic drug for fever and inflammation pain such as pain after traumas or dental. In spite of the wide used, (NSAIDs) caused a large variation of toxicity which may include severe nephrotoxicity, hepatotoxicity, and (GI) tract disorders. All classical (NSAIDs) inhibit biosynthesis of prostaglandin, MA shows the identical effect that may be accountable for the anti- inflammatory, antipyretic and, analgesic properties of all traditional drugs of (NSAIDs) [6]. Oxazine is aromatic heterocyclic six-membered compounds and it is containing the oxygen atom and the nitrogen atom are both present in their composition. [7]. 1,2-oxazine offered a wide range of recreational activities, such as antibacterial, paradises [8-9]. Triazole an aromatic heterocyclic compound which including 5 membered cyclic system containing in their structure the 2 carbon atoms and 3 nitrogen atoms and has 2 isomers, which are very important compounds in medical and pharmaceutical chemistry and are considered to be among the compounds involved in the pharmaceutical industry [10-13].

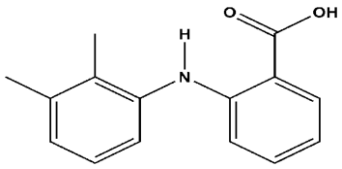


Figure 1. Chemical structure of Mefenamic acid

Experimental

Merck chemicals were purified and BDH was employed with KBr disk, "Testseon Shimadzu (FT- IR 8400Series Japan). The ^{1}HNMR spectra were obtained using DMSO as the solvent and TMS as the internal standard (Bruker, Ultra Shield 500 MHZ Switzerland).

Synthesis of 1- 2-((2,3-dimethylphenyl) amino) benzoyl chloride (M1) [6]

In 50 ml a round bottom flask with a reflux condenser, 0.01 mol of compound (M) was dissolved in 75 mL of $SOCl_2$, for 3 h and then the oil product was collected (Table 1).

Synthesis of 2-(2-((2,3-dimethylphenyl) amino) benzoyl) hydrazine-1-carboxamide (M2) [4]

(0.03 mol) of hydrazine carboxamide and the 10% NaOH (75 mL) solution is mixed with stirring for 20 minutes. In 50 mL of dioxane, a mixture of (0.01 mol) of compound (M1) was dissolved dropwise for 30 minutes. With stirring for 24 h, ice water is added to the mixture, stirred for 30 minutes and acidified with HCl. The progress of the interaction was monitored by TLC. (Table 1).

Synthesis of 5-(2-((2,3-dimethylphenyl) amino) phenyl)-4H-1,2,4-triazol-3-ol (M3) [3]

For four hours, a combination of compound (W2) (0.01 mol) and NaOH 4% (0.03 mol) was refluxed and stirred and the mixture was allowed to be cool. The TLC was used to monitor the process while it was acidified with concentrated HCl and recrystallized from 100% ethyl alcohol. (Table 1).

Synthesis of 2-((2,3-dimethylphenyl) amino)-N'-phenylbenzohydrazide (M4) [10]

In a round bottom flask, 0.01mol of compound (M) was added, followed by a mixture of phenyl hydrazine (0.02 mol) and ethanol (40 ml). The mixture was then refluxed with stirring for five to six hours, after which the precipitate was dried and recrystallized from absolute ethyl alcohol (Table 1).

Synthesis of 5-(2-((2,3-dimethylphenyl) amino) phenyl)-4-(phenylamino)-4H-1,2,4-triazole-3-thiol (M5) [1]

Compound (M4) (0.01 mol) and CS_2 (0.02 mol, 1.52 mL) were mixed together with KOH (0.02 mol, 1.12 g) and ethyl alcohol (20 mL) for 12 h washing with diethyl ether and purified via water (10 mL) and then adding NH_2NH_2 80 % (0.02 mol, 0.64 g) for 1 h. The product was cooled and acidified with acetic acid, the excess solvent was evaporated with a rotary evaporator, TLC was used to trace the process, and 100% ethanol was recrystallized (Table 1).

Synthesis of (2-((2,3-dimethylphenyl) amino) benzoyl) glycine (M6) [4]

After that, a stirring solution of 3-aminopropanic acid (0.03 mol, 2.25 g) and NaOH was added to the compound (M5) (0.01 mol, 4.69 g) dissolved in dioxane (5 mL) and stirred overnight and then acidified with concentrated HCl. The solution was concentrated using a rotary evaporator. The response was monitored using TLC. After that, the remaining precipitate was dissolved in ethanol (Table 1).

Synthesis of (E)-2-(2-((2,3-dimethylphenyl) amino) phenyl)-5-styryl-2,5-dihydro-6H-1,3-oxazin-6-one (M7) [2]

Benzaldehyde (0.03 mol) was added to a combination of compounds (M6) (0.01 mol) with CH_3COOH (20 mL) and $(CH_3COO)_2O$ (80mL) and the mixture was refluxed for 6-7 h.TLC was employed to monitor the process, and absolute ethyl alcohol was recrystallized (Table 1).

Table 1. Some of physical properties of compounds (M1-M7)

Com. NO.	Molecular Formula	M.Wt	Color	m.p. °C	Yield%	Rf	(TLC)
M1	$C_{15}H_{14}ClNO$	259	Reddish-brown	Oily	97	--	--
M2	$C_{16}H_{18}N_4O_2$	314	Off -white	166-168	93	0.77	Acetone: n-hexane 1:2
M3	$C_{16}H_{16}N_4O$	296	Light brown	190-192	64	0.65	Benzene: acetone1:1
M4	$C_{21}H_{21}N_3O$	255	Green Yellowish	176-179	69	0.68	Acetone: n-hexane 1:2
M5	$C_{22}H_{21}N_5S$	311	Reddih Brown	190-192	54	0.7	Acetone: n-hexane 1:2
M6	$C_{18}H_{20}N_2O_3$	298	Yellow	188-189	64	0.62	n-hexane: $CHCl_3$ 1:1
M7	$C_{26}H_{24}N_2O_2$	384	Black	298 -202	86	0.76	petrolum ether: $CHCl_3$ 1:1

Results and discussion

Spectral investigation of Compound (M1)

The FTIR spectrum of M1) is shown in Figure 2. Compound M1 is identified by the appearance of OH band of carboxylic acid in (M) at 3404 -2400 cm^{-1} and the appearance of a new band at 1772 cm^{-1} that refers to the carbonyl group of acid chloride, NH at 3212 cm^{-1}, CH_{ar} at 3021 cm^{-1}, CH_{alph} at 2947-2826 cm^{-1}, C=C group at 1577cm-1-1492 cm^{-1}, C-N at 1353 cm^{-1}, C-O group at 1224-1246 cm^{-1}, and C-O group at 1224-1246 cm^{-1}.

Spectral investigation of Compound (M2)

The FTIR spectrum of M2 is shown in Figure 3. The compound M2 is identified by the appearance of CO-Cl at 1772 cm^{-1}, NH_2 at 3307 cm^{-1} and NH at 3214 cm^{-1}, C-H_{ar} at 3008 cm^{-1}, CH_{alph} at 2850-2975 cm^{-1}, C=C_{ar} at 1573 cm^{-1}, NH-C=O at 1647 cm^{-1}, C-N at 1358 cm^{-1}, and C-O at (1191- 1256 cm^{-1}.

^{1}HNMR spectrum of the compound M2 is shown in Figure 4. Singlet peaks at 3.57 ppm owing to CH_3 and at 7.39-7.82 ppm is for $CH_{ar.}$ Peak at 8.09 ppm is owed to O=C-NH, 8.23 ppm for (NH_2), 2.02 ppm of O =C-NH, and 2.04 ppm of NH.

Spectral investigation of Compound (M3)

The FTIR spectrum of M3 is shown in Figure 5. Compound M3 is identified by appearance of NH group at 3248 cm^{-1}, OH group at 3413 cm^{-1}, C=C at 1588 cm^{-1}, CH_{alph} at 2922-2985cm^{-1}, CH_{ar} at 3081 cm^{-1}, C=N at 1620 cm^{-1}, C-N at 1360 cm^{-1}, 1220-1269 cm^{-1} to C-O.

^{1}HNMR spectrum of M3 is shown in Figure 6. Signals appeared are attribute to CH_3 at 3.79 ppm, $CH_{ar.}$ at 7.39-8.10 ppm, OH at 10.48 ppm, NH_{trizol} at 11.52 ppm, NH at 8.73 ppm.

^{13}CNMR spectrum of M3 is shown in Figure 7. Signals at 50.79 ppm and 50.00 are related

to C-triazol, C_{ar} at 127.75-142.84 ppm, 158.02 ppm of C-OH in triazol ring, 50.52 ppm of CH_3 and NH at 161.95 ppm.

Spectral investigation of Compound (M4)

The FTIR spectrum of M4 is shown in Figure 8. OH, band of COOH in (M) is at 3448-2400 cm^{-1}, NH at 3266- 3175 cm^{-1}, CONH at 1626 cm^{-1}, C=C at 1588 cm^{-1}, CH_{alph} at 2992-2864 cm^{-1}, CH_{ar} at 3075 cm^{-1}, C-N at 1337 cm^{-1}, C-O at 1196-1307 cm^{-1}.

^{1}HNMR spectrum of M4 is shown in Figure 9 which demonstrated that the singlet signal of OH had vanished OH at 11.07 ppm in carboxylic group of (M), NH at 8.67 ppm, O=C-NH at 8.71 ppm and CH_3 at 3.45 ppm, and $(CH)_{ar.}$ at 7.46-7.89 ppm.

Spectral investigation of Compound (M5)

The FTIR spectrum of M5 is shown in Figure 10. It is shown that SH group is at 2063.83 cm^{-1}, NH at 3317- 3290 cm^{-1}, $C=C_{ar}$ at 1519 cm^{-1}, C=N at 1677 cm^{-1}, CH_{alph} at 2959-1868 cm^{-1}, CH_{ar} at 3090- 1408cm^{-1}, C-N at 1245,1287 cm^{-1}.

^{1}HNMR spectrum of M5 is shown in Figure 11. Appeared signals are for NH at 8.30 ppm, and CH_3 at 3.74 ppm, and CH_{ar} at 7.21-7.73 ppm, SH at 13.73 ppm.

^{13}CNMR spectrum of M5 is shown in Figure 12. Signal at 51.46 is related to NH-C, $CH_{ar.}$ at 125.90-135.89 ppm, C-SH at 178.34 ppm, N=C -N at 159.48 ppm.

Spectral investigation of Compound (M6)

The FTIR spectrum of M6 in shown in Figure 13. The compound M6 is identified by appearance of oH band of COOH at 3433-2622 cm^{-1}, NH at 3204- 3122 cm^{-1}, C=O acid and amide at 1710 cm^{-1} and 1625 cm^{-1}, $C=C_{ar}$ at 1544 cm^{-1}, CH_{alph} at 2970- 2857 cm^{-1}, CH_{ar} at 3031 cm^{-1}, 1382 cm^{-1} to C-N, C-O at 1218 -1268 cm^{-1}.

^{1}H-NMR spectrum of M6 is shown in Figure 14. Signals of $HN\text{-}CH_2COOH$ at 4.65 ppm, N-NH, at 2.05 ppm, CH_3 at 3.65 ppm, CH_{ar} at 7.34- 8.15, $O=C\text{-}NH\text{-}CH_2$ at 8.73 ppm, and signal OH of COOH group at 11.47 ppm are shown respectively.

Spectral investigation of Compound (M7)

The IR spectrum of M7 is shown in Figure 15. OH, of acid at 3433-2400 cm^{-1}) and C=N at 1586 cm^{-1}, 3266 cm^{-1} to NH, CH at 2938-2864 cm^{-1}, CH_{ar} at 3006 cm^{-1}, C=O ester at 1731 cm^{-1}, 1492 cm^{-1} to C=C, C-N at 1335 cm^{-1} and C-O at 1205 cm^{-1} are represented.

^{1}HNMR spectrum of M7 is represented in Figure 16 showing that CH_3 signal at 3.63ppm, $CH_{ar.}$ at 7.47-7.63 ppm, s,3H CH=C, s,2HCH=C at 7.65 ppm, 7.90 ppm and NH at 7.53 ppm are appeared.

^{13}CNMR spectrum of M7 is shown in Figure 17, representing CH=C signal are appeared at 113.51 ppm, 113.51 ppm, $CH_{ar.}$ at 123.51-135.21 ppm,128.90 ppm-135.82 ppm, Coxazol ring at 131.65 ppm, C=O at 169.07-169.08 ppm, O-C=N at 171.07- 169.14 ppm, and C-NH at 168.59 ppm.

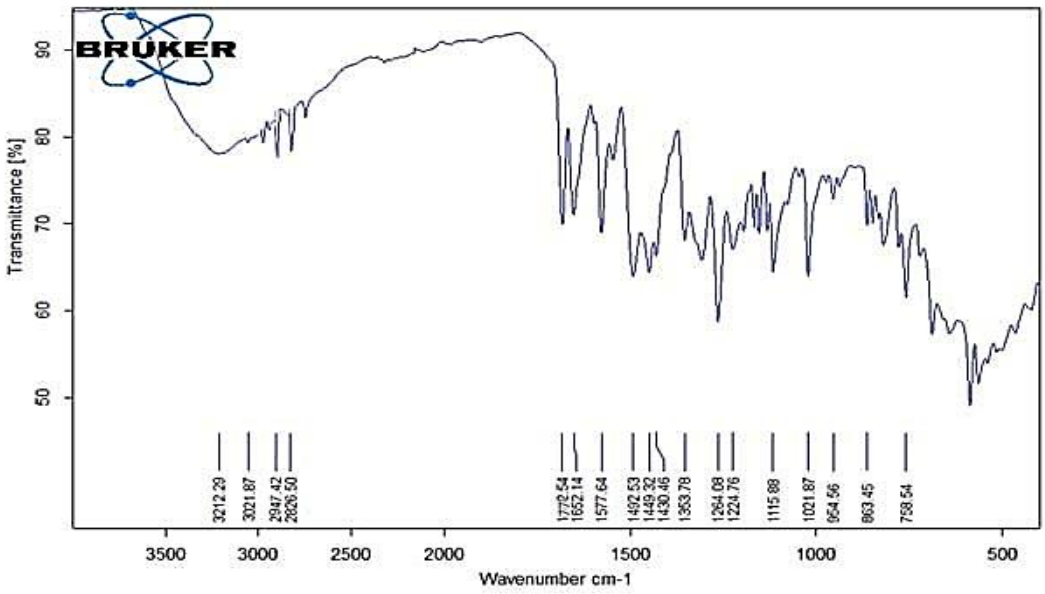


Figure 2**.** FTIR spectrum of M1

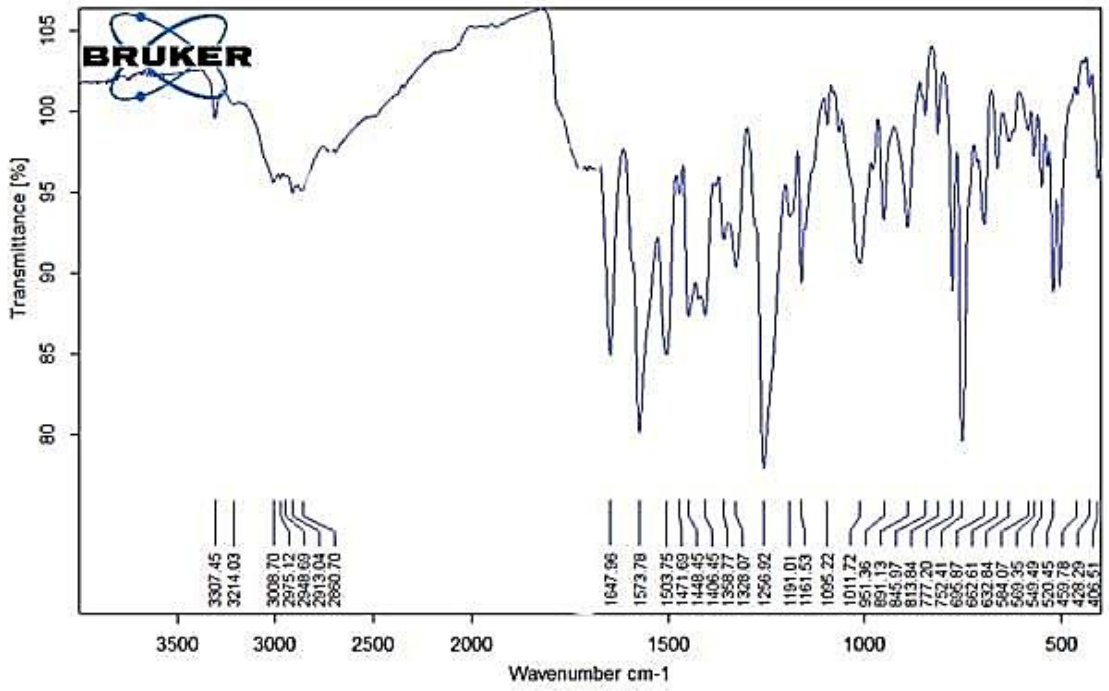


Figure 3. FTIR spectrum of M2

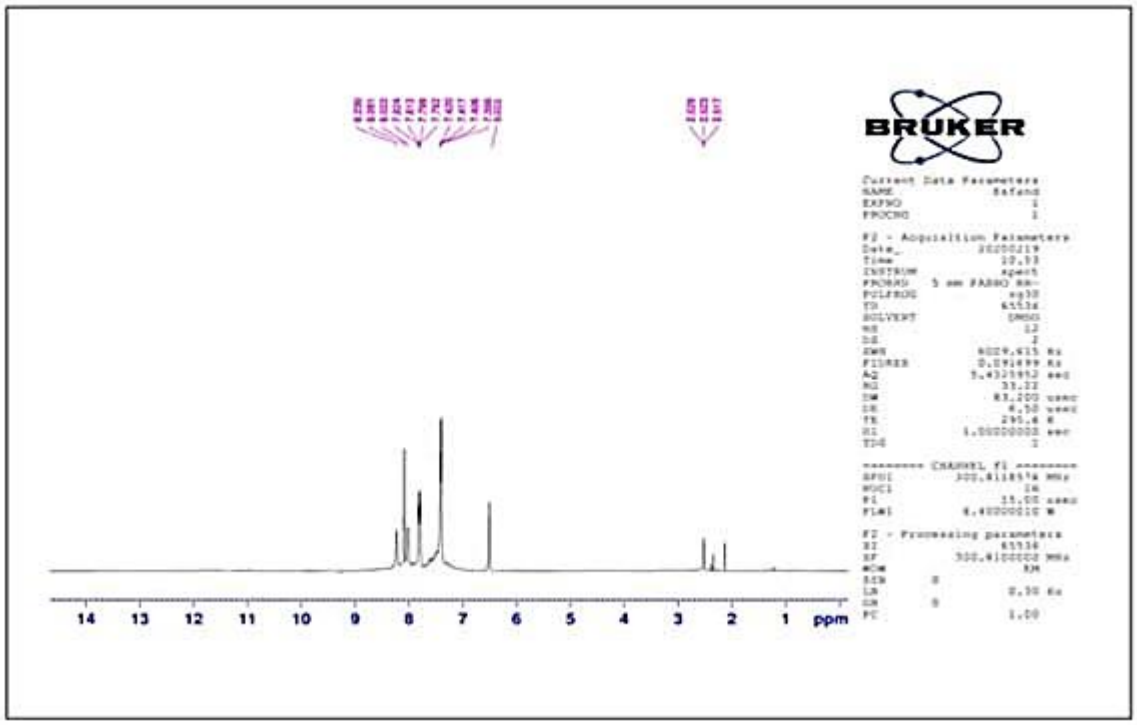


Figure 4. [1]HNMR spectrum of M2

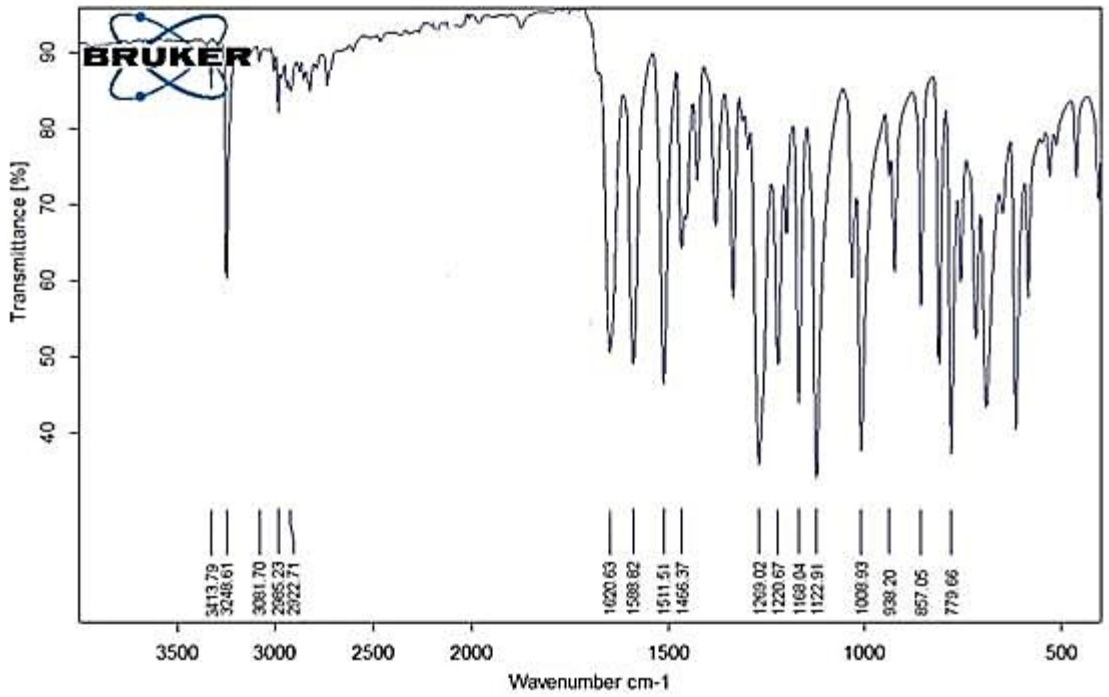


Figure 5. FT-IR spectrum of M3

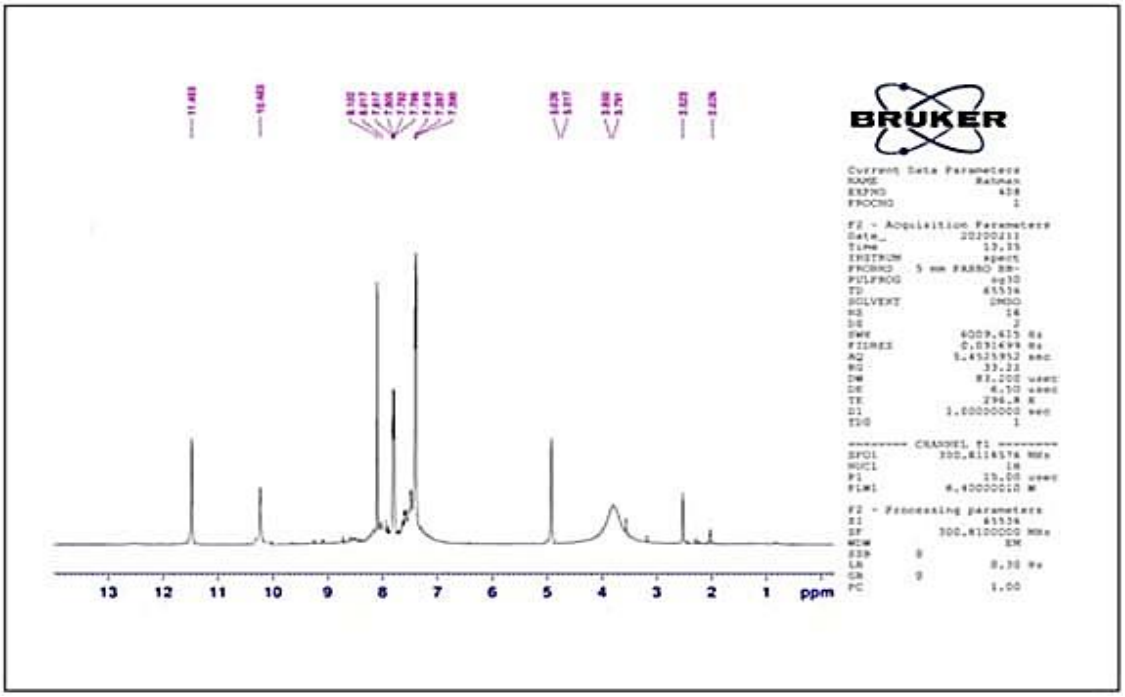


Figure 6. [1]HNMR spectrum of M3

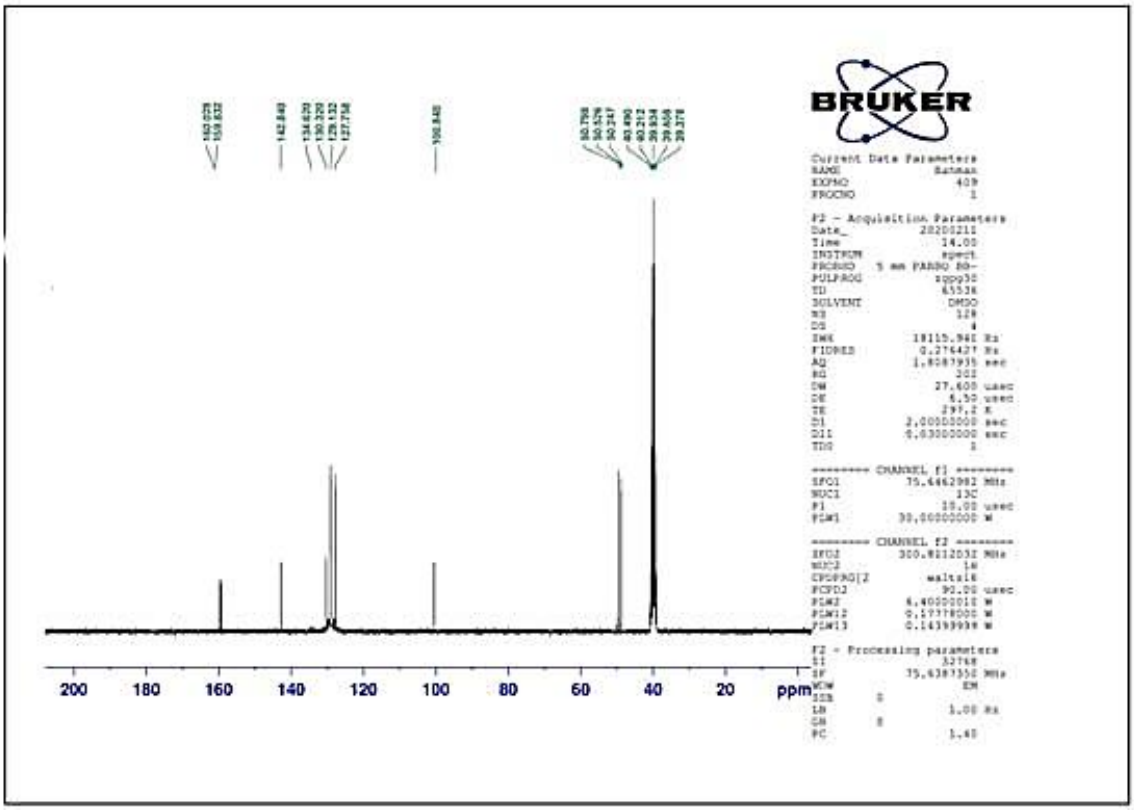


Figure 7. [13]CNMR spectrum of M3

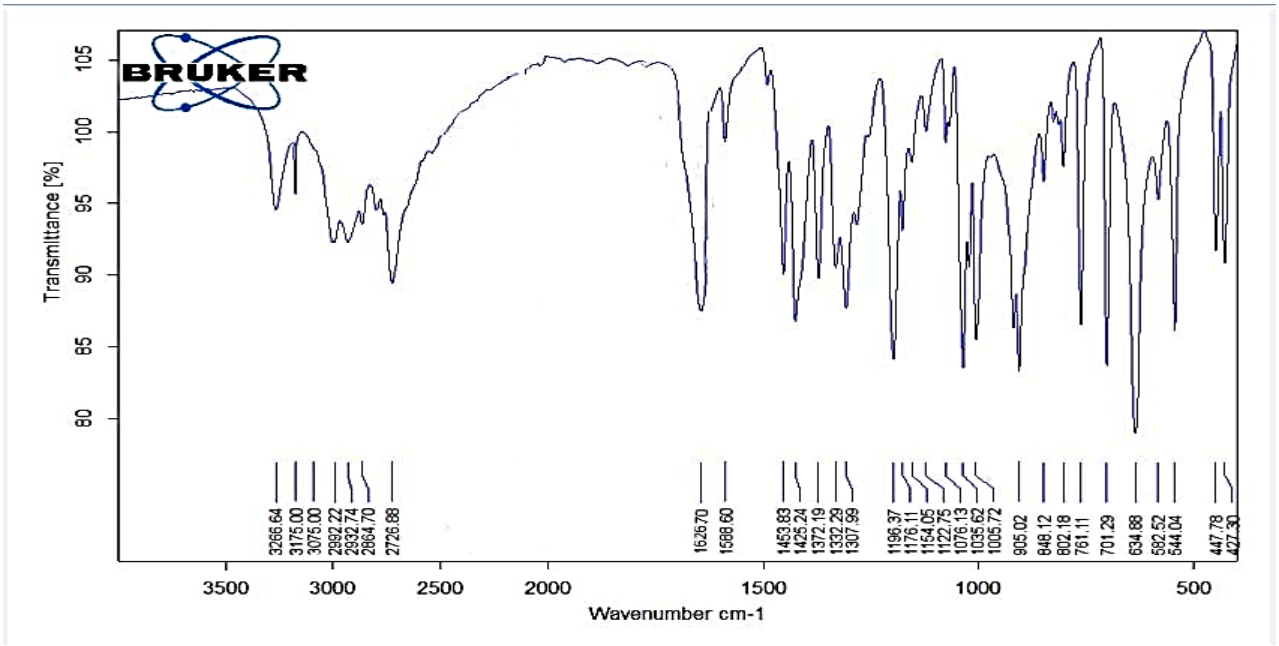


Figure 8. FT-IR spectrum of M4

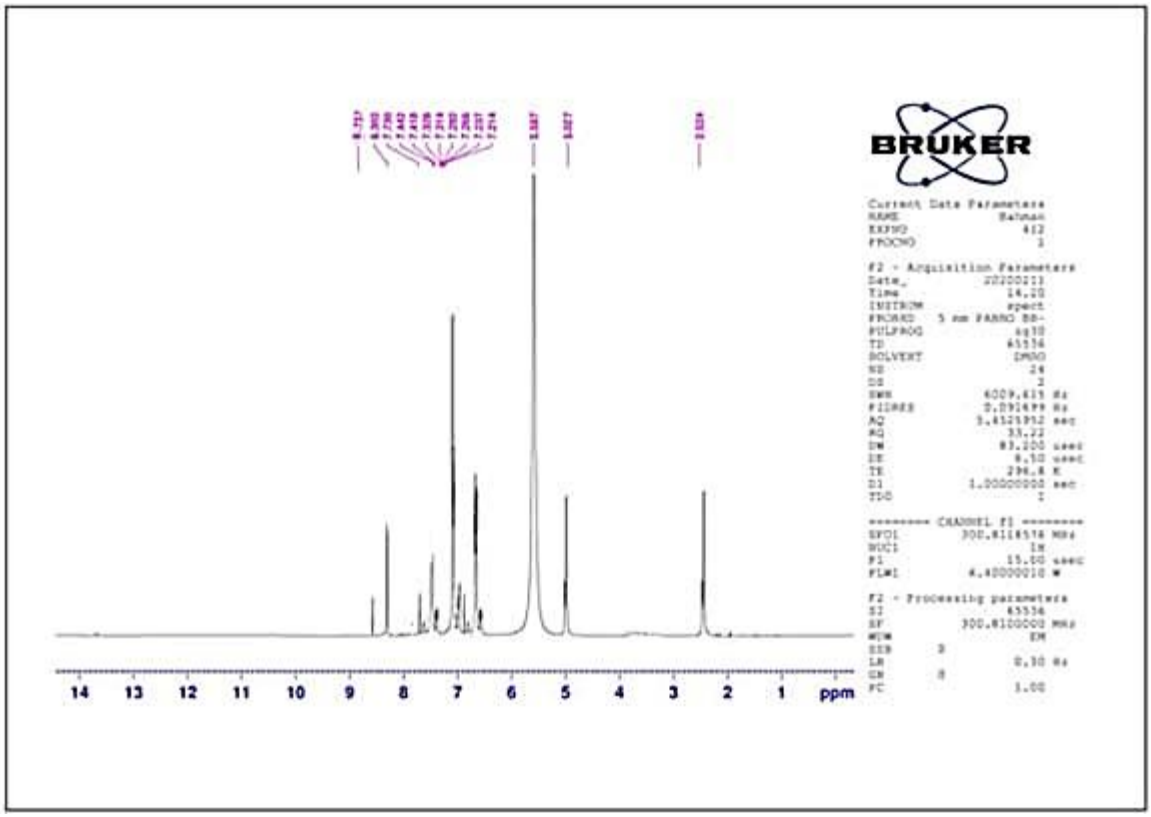


Figure 9. [1]HNMR spectrum of M4

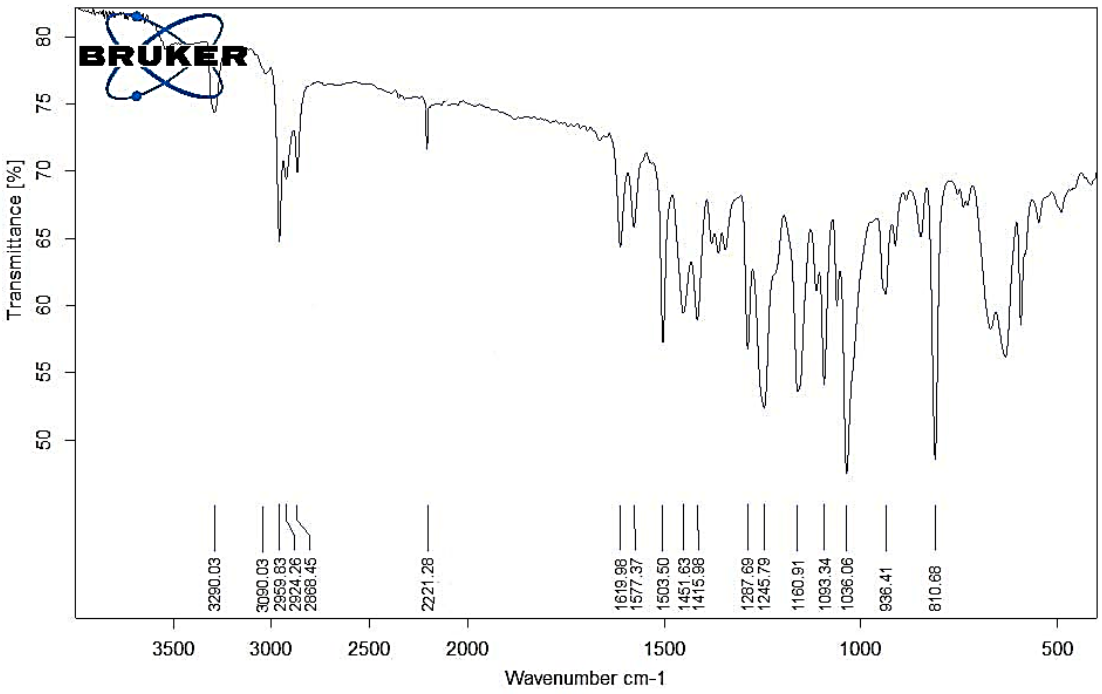


Figure 10. FTIR spectrum of M5

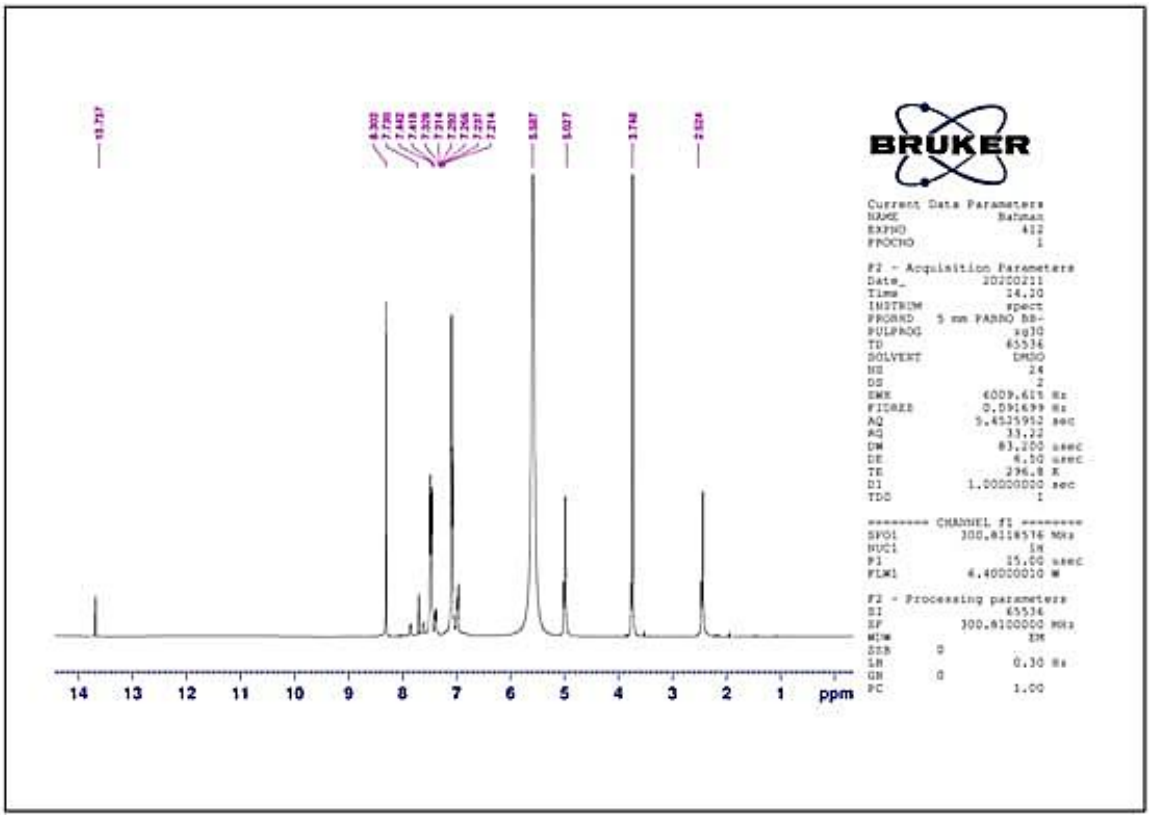


Figure 11. [1]HNMR spectrum of M5

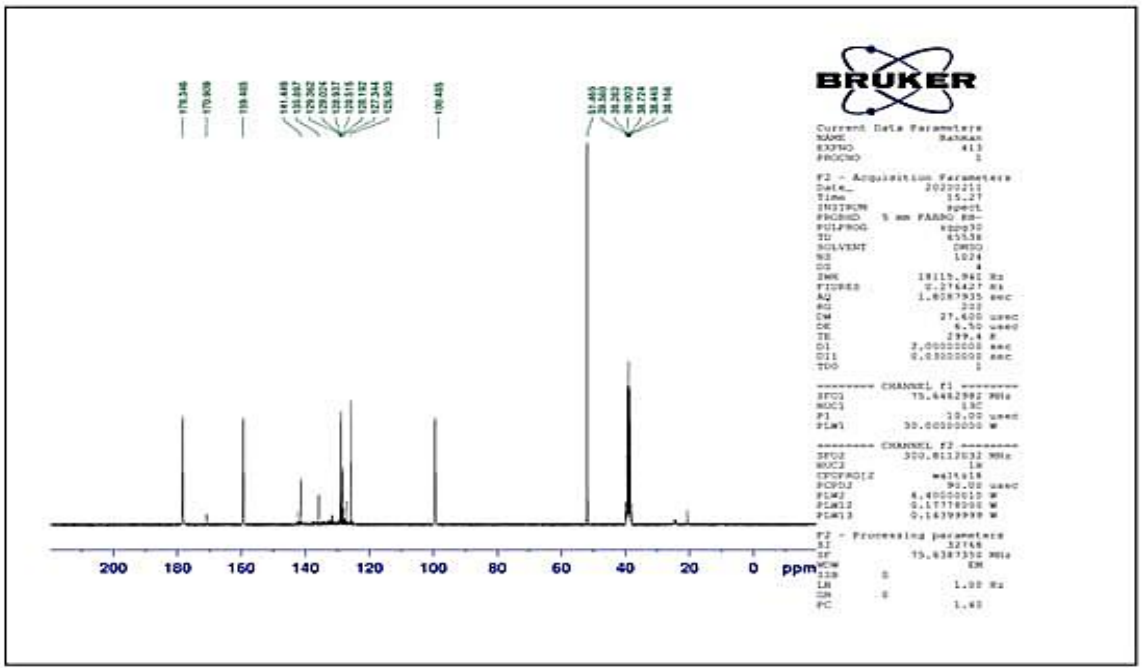


Figure12. ^{13}CNMR spectrum of M5

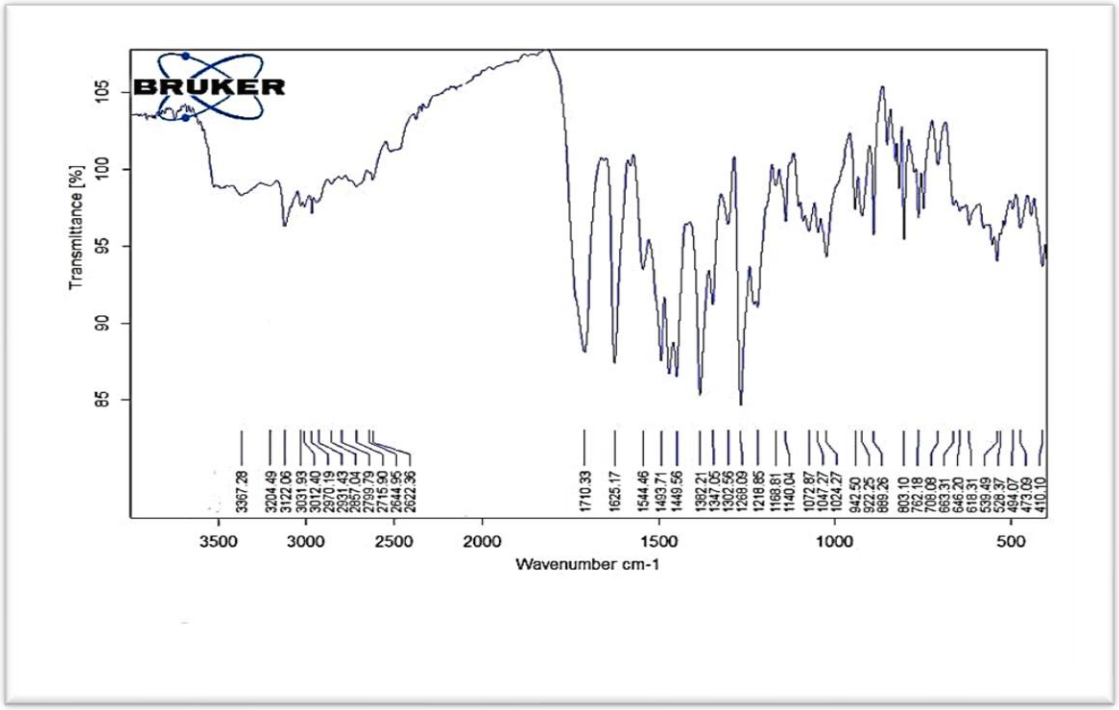


Figure 13. FTIR spectrum of M6

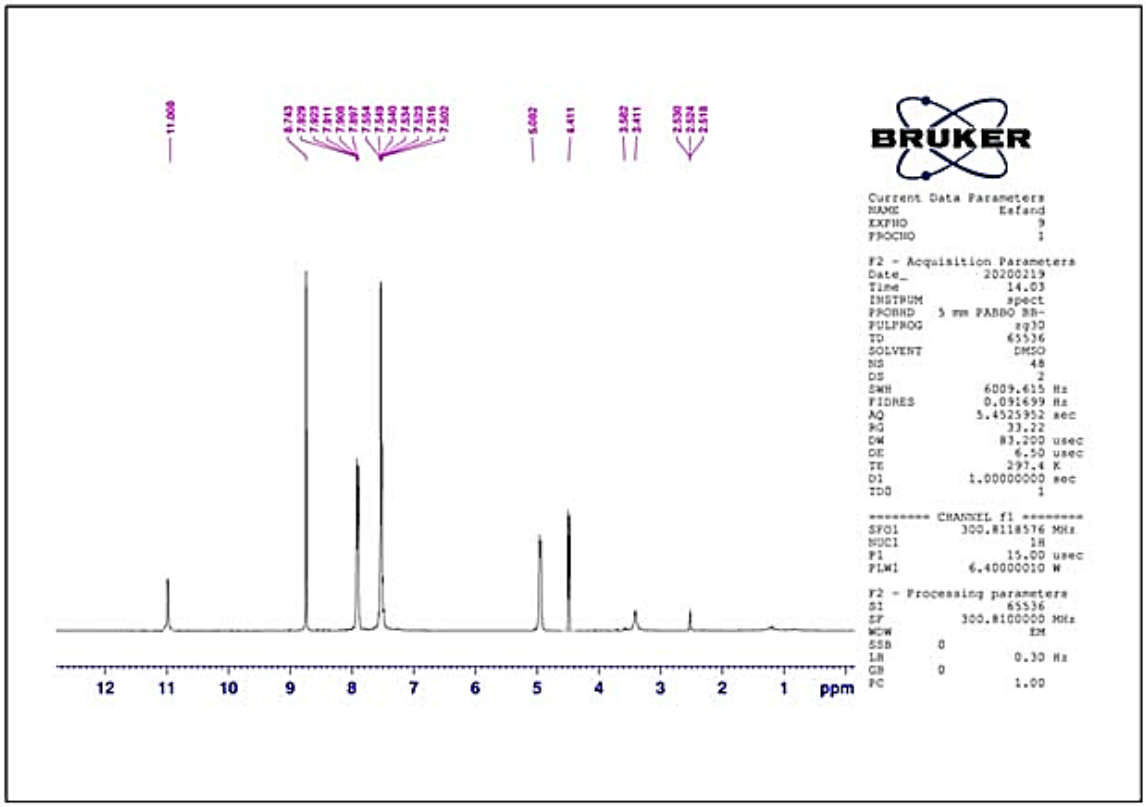


Figure 14. [1]HNMR spectrum of M6

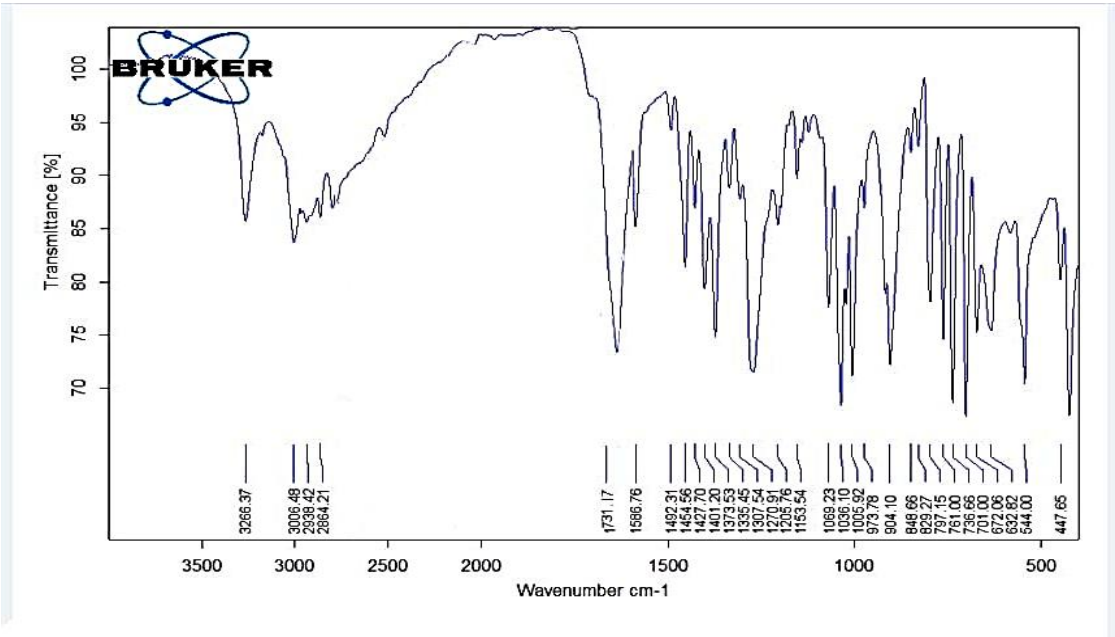


Figure 15. FTIR spectrum of M7

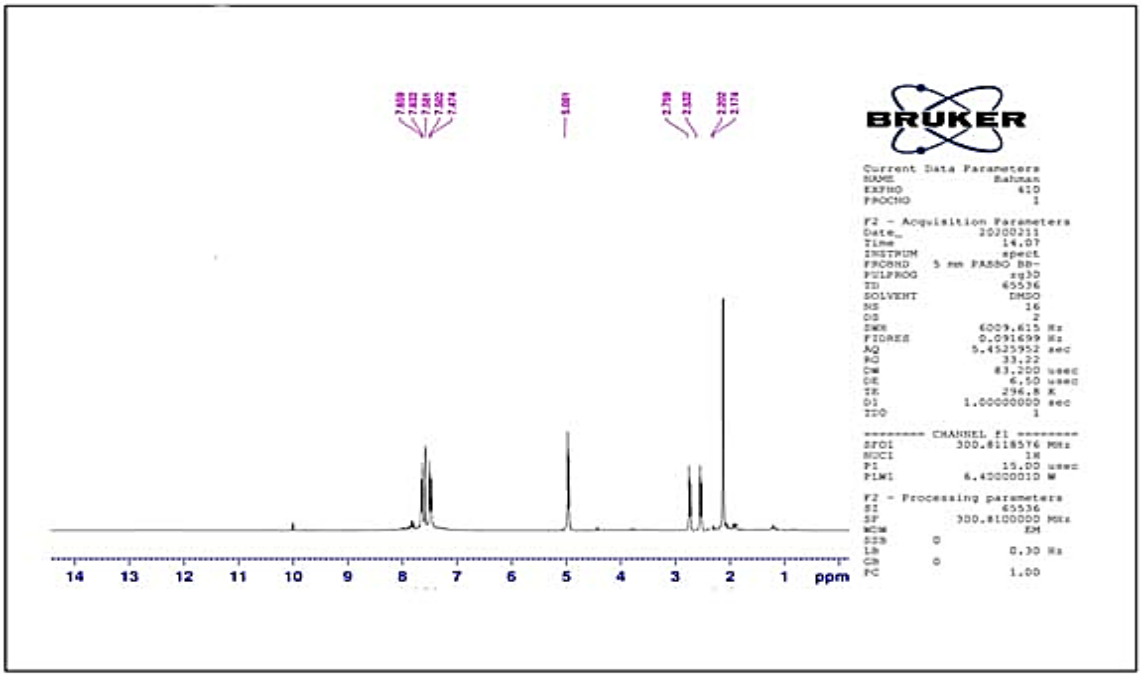


Figure 16. [1]HNMR spectrum of M7

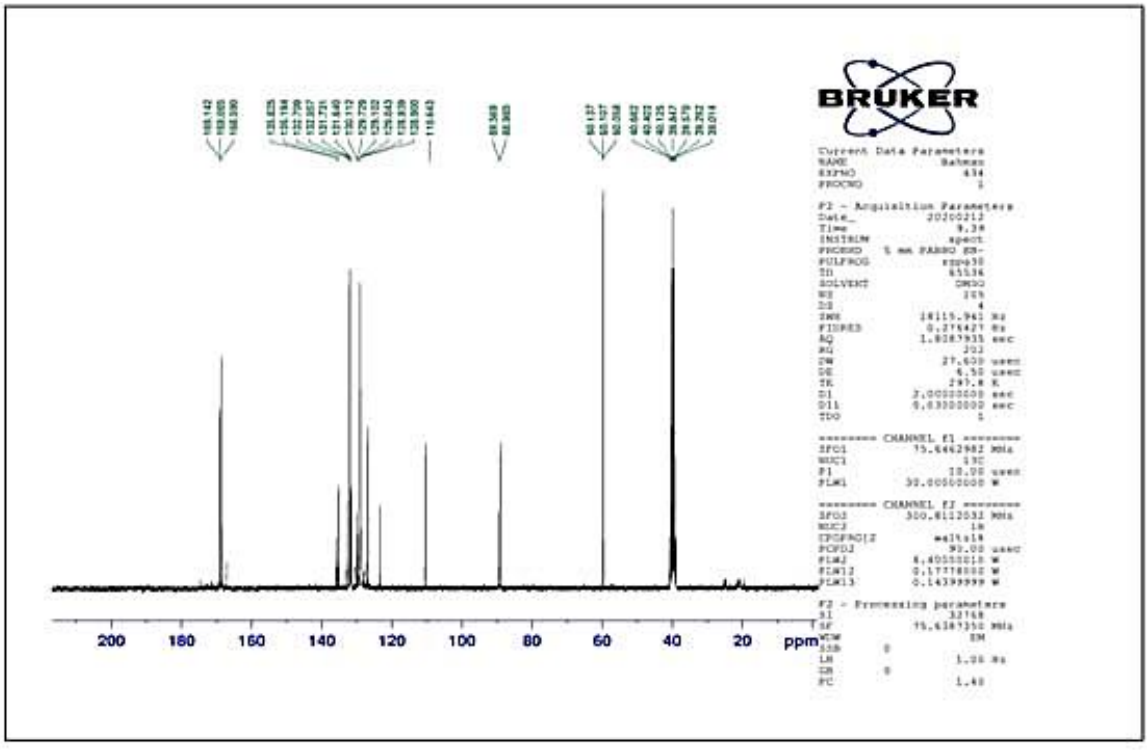
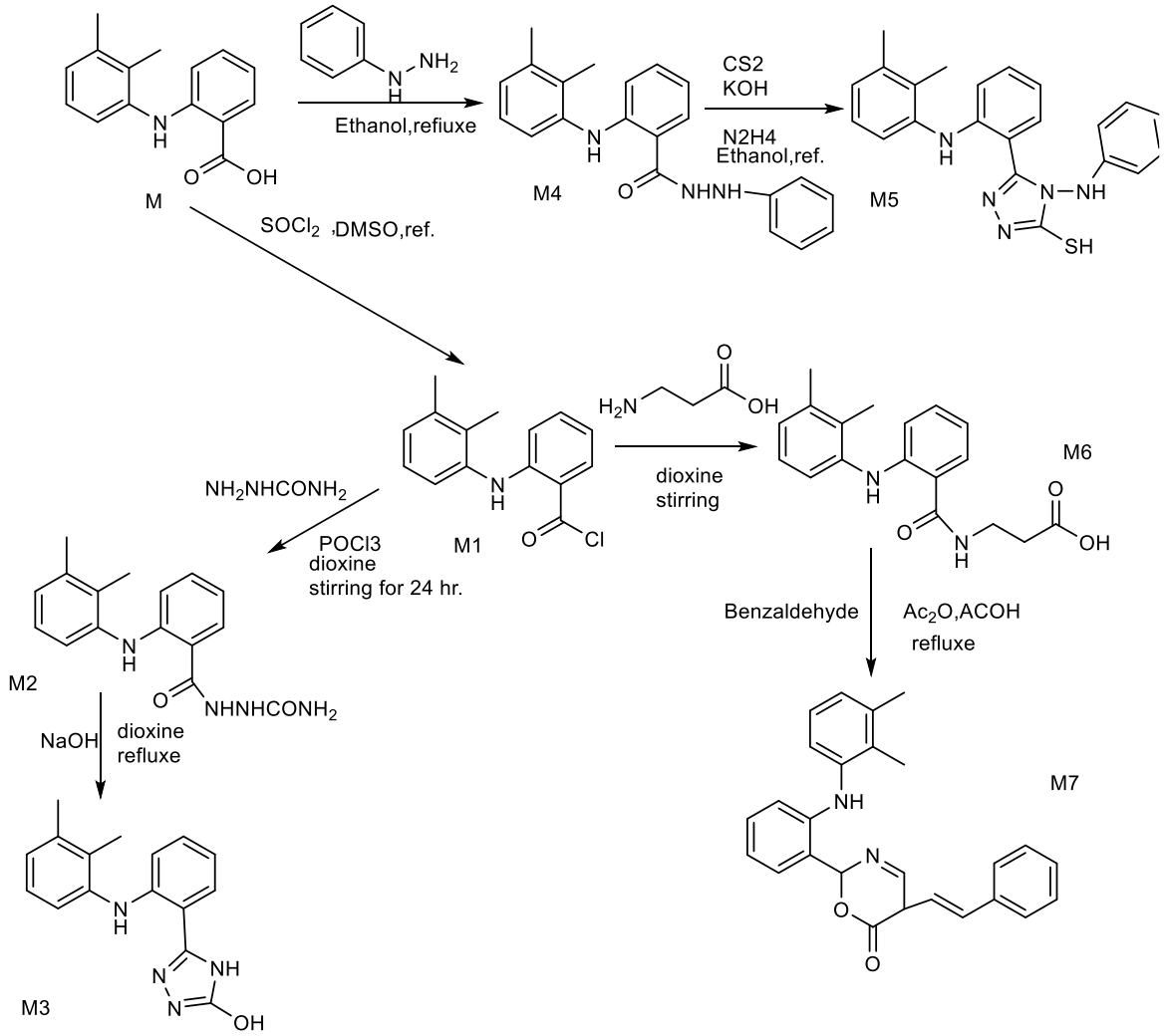


Figure 17. [13]CNMR spectrum of M7



Scheme 1. Synthesis of Compounds M1-M7

Biological productivity

The biological activity was studied E. coli (G-) and Staph. Aureus (G+) are two species of bacteria, the compounds (M2, M3, M4, M5, M6) were found to inhibit the growth of(G-), the compounds (M2, M3, M6, M7) were found to have high activity against (G+), when compared with the biological activity of ciprofloxacin.

Table 2. The biological activity of (M1-M7) compounds

Comp. No.	Escherichia coli	Staphylococcus aureus
Ciprofloxacin (Antibiotic) Standard	12	18
M1	10	16
M2	14	20
M3	12	18
M4	15	14
M5	14	10
M6	28	24
M7	10	25

Figure 18**.** Biological Effect of compounds

Antioxidant Action

The standard DPPH approach was used to perform the antioxidant operation on the compounds. [13]. A standard solution of DPPH (1.3 mg/mL) was prepared in MeOH, and 100 mL DPPH was added to 3 mL MeOH. (25, 50, 75, and 100 µg\mL) were prepared, the tubes were exposed to light for 30 minutes and the absorbance was measured at 517 nm on a "UV-VIS spectrophotometer. Figure 19 and Table 3, showed the compounds (M1-M7) have moderate to high antioxidant activity due to OH, NH and SH groups with compared to normal (ascorbic acid) activity (IC50=31.95 µg\mL).

Table 3. Antioxidant activity of (M1-M7) compounds

Conc. µg\mL	M1	M2	M3	M4	M5	M6	M7	STD (Ascorbic acid)
25	46.76	49.41	51.34	41.44	46.35	40.42	38.24	46.12
50	47.83	56.42	58.21	50.25	59.22	41.63	59.52	60.14
75	50.77	61.26	67.23	61.32	60.16	59.73	62.7	65.01
100	66.21	68.44	73.11	70.65	67.18	66.22	69.81	78.3
IC50 µg\mL	43.09	29.82	24.91	48.72	34.24	58.28	45.11	31.95

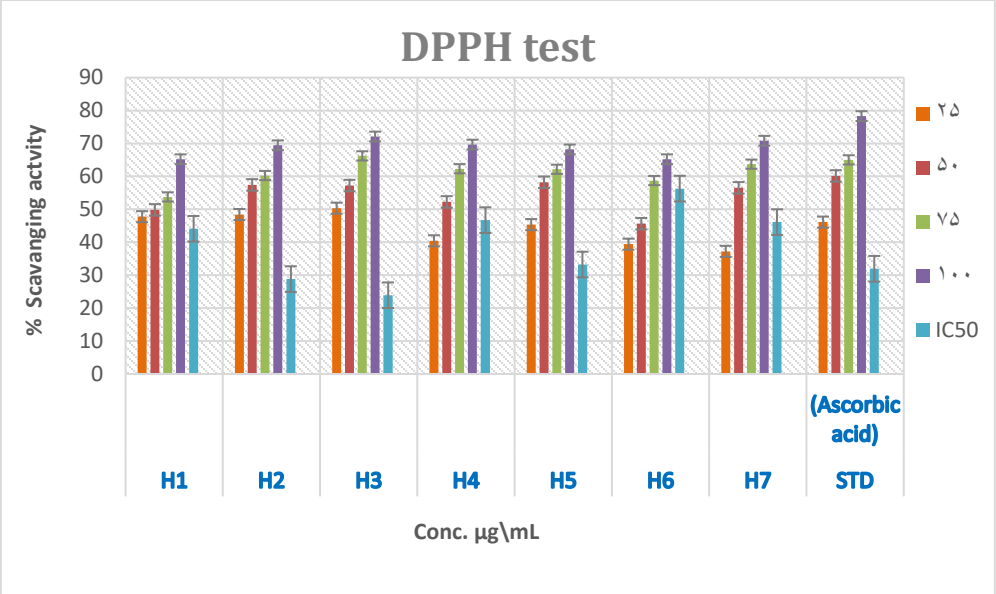


Figure 19. DPPH test of compounds (M1-M7).

Conclusion

New derivatives can be prepared due to the presence of effective groups The ratio of productions was good and useful for the continuation of the next step. Compounds possess significant antioxidant and antibacterial activity.

Acknowledgements

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Conflict of Interest

No conflict of interest was declared by the authors.

Disclosure statement

No potential conflict of interest was reported by the authors

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Graphical abstract